

**REMARKS**

Claims 1-10, 20, and 25-29 were previously pending in this application. By this amendment, claims 1-10, 20, 25-28 have been amended. Support for the amendment of claim 20 to depend from claim 7 is provided at least in the claims as originally filed. Support for the amendment of claim 7 can be found in claim 7 as originally filed. Support for the amendment of claim 8 can be found at least in Experimental 2 as originally filed. Support for the amendment of claims 9 and 10 can be found at least in claims 9 and 10 as originally filed. Support for the amendment of claims 1, 2, 20, 25 and 26 can be found at least at page 14, line 19 to page 22, line 4 of the specification as filed and support for the amendment of claim 25 can also be found at least in claim 28 as originally filed. Applicants have also amended claims 25, 27, and 29 to remove the reference to Figures that include non-elected sequences and to add the SEQ ID NOs: of the sequences referred to in the claims. No new matter has been added. Claims 11-19, 21-24, 28, and 30-47 have been cancelled.

As a result, claims 1-10, 20, 25-27, and 29 are pending for examination with claims 1, 2, 7, 8, and 25 being independent claims. No new matter has been added.

**Objections****In the Specification**

Applicants have amended the specification to address the Examiner's objection to the priority claim made in the preliminary amendment and to include reference to the application as a national stage filing under 35 U.S.C. §371 of international application PCT/EP98/08543, filed December 17, 1998. Applicants submit that these corrections overcome the Examiners objections to the priority claim.

Applicants will provide a new oath or declaration in compliance with 37 C.F.R. 1.67(a). A corrected document has been prepared and will be filed with the USPTO when executed by Applicants.

Applicants have amended the specification to remove material added in the preliminary amendment describing the incorporation by reference of the entire contents of GB 9726804.9 and all references disclosed herein.

Applicants have replaced each hyperlink in the specification with the name and mailing address of the organization hosting/sponsoring the corresponding website. No new matter has been added.

### **In the Claims**

Applicants have amended claim 20 to depend from pending claim 7.

### **Rejections Under 35 U.S.C. §101**

The Examiner has rejected claims 1-6 and 20 under 35 U.S.C. §101 as failing to set forth steps involved in the process claimed. Applicants have amended claims 1, 2, and 20 to add steps involved in the claimed methods. On the basis of the amendments to the claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-6 and 20 under 35 U.S.C. §101.

### **Rejections Under 35 U.S. C. §112, First Paragraph**

The Examiner rejected claims 1-10, 20, and 25-29 as failing to comply with the enablement requirement. Applicants have amended claims 1-6, 20, 25-26, and 28.

In rejecting claims 1-10, 20 and 25-29, the Examiner states the factors necessary for enablement analysis. The Examiner indicates that based on the application as filed and the state of the art, it is unpredictable as to whether one of skill in the art could make and use applicants' invention. Applicants respectfully disagree with the Examiner's assertion and submit that the specification as filed does provide sufficient guidance to allow one of ordinary skill in the art to make and use the claimed invention without undue experimentation.

In paragraph 12 of the Office Action the Examiner questions whether an association actually exists between the region of chromosome 18q identified by Applicants and mood disorder. In particular, the Examiner contends that the specification discloses that the highest LOD score obtained for any marker in the region of chromosome 18q between markers D18S51 and D18S61 was 2.01, whereas the specification and the prior art teach that such a score is not indicative of linkage.

Applicants submit that the association between the region of chromosome 18q and mood disorder is supported in the specification at page 4, lines 10 to 22, which describes a study in which LOD score analysis was performed on family MAD 31, a Belgian family of a BP II proband. Although multi-point linkage analysis gave a maximum multi-point LOD score of +1.34, simulation studies indicated that this LOD score is well within the range of what can be expected for a linked marker given the information available in this family. The specification also states at page 4 lines 22-30 that “an affected sib-pair analysis also rejected the null-hypothesis of nonlinkage for several of the markers tested” and “two other groups also found evidence for linkage of bipolar disorders to 18q”. Thus, Applicants respectfully assert that the clear increase in LOD score values observed between the markers D18S346 and D18S979 (shown in Table 2) was considered a significant linkage at the time of filing.

The Examiner cites the Goossens et al., 2000 reference as indicating that no association between triplet repeats in the chromosome 18q region and bipolar disorder was found to exist. Applicants respectfully assert that Goossens *et al* 2000 reference deals only with a possible involvement of triplet nucleotide repeats, i.e. CAG/CTG repeats in bi-polar disorder, but the reference does not question the association of the 8.9 cM region with bi-polar disorder. Thus, the Goossens reference does not indicate a lack of an association between the region of chromosome 18q region cited in the instant claims and mood disorder.

Applicants respectfully submit that based on the evidence presented in the application as filed, including the LOD score analysis for the family MAD31, one of ordinary skill would recognize the existence of an association between the 8.9 cM region of chromosome 18q recited in claim 1 and mood disorder.

With respect to the breadth of the claims, the Examiner maintains in paragraph 12 of the Office Action that it is unpredictable as to whether an association exists with any type of mood disorder other than bipolar disorder. Applicants respectfully disagree with this conclusion and submit that members of family MAD31, in which the genetic association study was carried out, manifest a range of clinical diagnoses, in addition to the type II bipolar illness present in the

proband. In summary, family MAD31 contains two members with type II bipolar illness (BP II), one with type I bipolar illness (BPI), two with recurrent unipolar illness (UP), one with major depressive disorder (MDD), one with the manic subtype of schizoaffective disorder (SAm) and one with the depressive subtype of schizoaffective disorder (SAd) (see Experimental 1 page 24, line 31 to page 25 line 7). BP II, BPI, UP, MDD, SAm and SAd may be collectively referred to as "BP Spectrum disorders", whereas UP, MDD, SAm and SAd are referred to as "BP-related disorders".

Applicants assert that one of ordinary skill would have recognized that, to a certain extent, the "mood disorders" can be viewed as different forms of a shared and complex biological condition, rather than a collection of distinct and separate conditions. Therefore, it is likely that the mood disorders share common genetic basis. Applicants attach herewith a report issued by the Johns Hopkins Department of Psychiatry and Behavioural Sciences in January 2002, which confirms that according to current thinking the "mood disorders" may be considered as different forms of a shared condition, encompassing the bipolar spectrum disorders and also such conditions as panic disorder. Therefore, Applicants assert that because Applicants have shown a genetic association within family MAD31, one of ordinary skill in the art would reasonably assume an association with "mood disorders" in general.

Additional support for breadth of the claims is provided with regard to the association with schizophrenia. As described in Experimental 1, a member of family MAD31 manifests schizoaffective disorder, the symptoms of which are believed to be a combination of elements of mood (affective) disorder and schizophrenia. It is extremely difficult to distinguish between schizoaffective disorder and schizophrenia. Therefore, the inventors believed at the time the application was filed that there was an association between chromosome 18q and schizophrenia.

Applicants submit that sufficient evidence of an association between mood disorders in addition to bi-polar disorder is provided in the specification as filed to indicate that contrary to the Examiner's conclusion, it would not be "completely unpredictable as to whether an association existed with any other type of mood or related disorder" (Office action, paragraph

12). Particularly in view of the high level of skill in the art, as acknowledged by the Examiner, Applicants respectfully assert that the teaching provided in the specification would allow one of ordinary skill in the art to make and use the invention as claimed without undue experimentation, and therefore the requirement for enablement has been met.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-10, 20, and 25-29 under 35 U.S.C. §112, first paragraph in view of the arguments and amendments made herein.

The Examiner has rejected claims 4 and 5 under 35 U.S.C. §112, first paragraph as lacking sufficient written description. Applicants respectfully traverse the rejection.

In paragraph 13 of the Office Action the Examiner contends that a deposit of the YAC clones is required in order to provide sufficient disclosure of the invention. However, Applicants submit that as indicated on page 26, lines 31 to 33 of the application as filed, the YAC clones referred to in the present application were all publicly available at the priority date of the present application and were obtained from the YAC Screening Centre, Leiden, The Netherlands or from CEPH, Paris, France. In these public collections the YAC clones are referred using the nomenclature used in claims 4 and 5. Accordingly, Applicants assert that based on the teaching provided in the specification as filed, one of ordinary skill in the art would be able to obtain any of the YAC clones referred to in present claims 4 and 5. Therefore, Applicants respectfully submit contend that there is no need for a deposit for patent purposes in respect of these clones.

Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4 and 5 under 35 U.S.C. §112, first paragraph.

#### **Rejections Under 35 U.S. C. §112, Second Paragraph**

The Examiner has rejected claims 1-6, 20, and 25-27 under 35 U.S.C. §112, second paragraph as indefinite.

The Examiner states in paragraph 15 of the Office action that because “the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicants are intending to encompass”. Applicants have amended claims 1, 2, 20, 25, and 26 to add the

steps involved in the method/process. Applicants respectfully submit that the amendments to claims 1, 2, and 20 obviate the Examiner's rejection of claims 1-6, 20, and 25-27 under 35 U.S.C. §112, second paragraph.

The Examiner also rejected claim 6 as indefinite because it refers to particular types of disorders as classified in a reference manual. Applicants have amended claim 6 to remove the reference to the manual. Applicants submit that the disorders listed in the claim as filed are disorders that are recognized by those of ordinary skill in the art and inclusion of a reference to the manual in the claim as filed was not necessary to fully describe the subject matter claimed.

Based on the amendment to claim 6, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 6 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claims 7, 9, and 10 under 35 U.S.C. §112, second paragraph as "omitting essential steps". (Page 11, Office Action). Applicants have amended claim 7 to clarify the steps in the method. Based on the amendment to claim 7, Applicants believe claims 7, 9, and 10 to be in condition for allowance and respectfully request that the Examiner withdraw the rejection of claims 7, 9, and 10 under U.S.C. §112, second paragraph.

The Examiner has rejected claim 8 under 35 U.S.C. §112, second paragraph as "omitting essential steps". (Page 11, Office Action). Applicants have amended claim 8 to clarify the steps in the method. Applicants believe that claim 8 as amended is now in condition for allowance and respectfully request that the Examiner withdraw the rejection of claim 8 under U.S.C. §112, second paragraph.

The Examiner has rejected claims 9 and 10 as indefinite. The Examiner states on page 11 of the Office Action that the phrase "repeated triplet" lacks sufficient antecedent basis. Although Applicants submit that the term "repeated triplet" in claim 7 does provide a proper antecedent basis, Applicants have amended claims 9 and 10 to clarify the language and have replaced the phrase "repeated triplet" with the phrase "triplet repeat". Applicants respectfully request the

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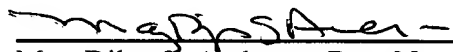
Examiner to reconsider and withdraw the rejection of claims 9 and 10 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claims 25-27 under 35 U.S.C. 112, second paragraph as being incomplete. Applicants have amended claim 25 to clarify the steps of the method. On the basis of the amendments to claim 25, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 25-27 under 35 U.S.C. §112, second paragraph.

### CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment that the application is not in condition for allowance, the Examiner is requested to contact the Applicant's representative at the telephone number listed below.

Respectfully submitted,  
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